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ARTICLE REVIEW

Medical nutrition therapy in enterocutaneous fistula: A step-by-step approach

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Abstract

As part of ECF management, nutrition plays a vital role in determining the prognosis as a predicator for both morbidity and mortality. Malnutrition can occur as a preceding situation or complication in ECF cases caused by the underlying disease, decreased food intake, increased protein requirements associated with systemic inflammation, and increased nutrient loss associated with the amount of fistula output. Therefore, nutrition management can act as prevention, therapy, or even both. The purpose of nutritional medical therapy in ECF cases is to adequately estimate nutritional needs, maintain fluid and electrolyte balance, and stimulate spontaneous ECF closure whenever possible. An analysis of nutrition needs has to be carried out individually by considering the etiology, the anatomical fistula location, and the amount of output. In the following article, we will discuss a comprehensive step-by-step nutrition treatment, by taking into account nutritional routes, macronutrient and micronutrient requirements, specific nutrients, pharmacotherapy, and monitoring and evaluation as to produce an optimal clinical outcome.

Keywords enterocutaneous fistula, malnutrition, nutrition

Introduction

Enterocutaneous fistula (ECF) incidence varies from 5 to 10% according to the etiology.[1] About 75% of ECF cases are adhered to iatrogenic causes which generally result from surgical complications, while the rest are linked to spontaneous causes such as inflammatory, radiation, and trauma conditions.[2,3] At the present, there is no incident data concerning ECF cases in Indonesia.

It is estimated that 50-90% of ECF patients experience nutritional problems, including malnutrition, dehydration, or electrolyte disorders.[4]

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Sepsis, malnutrition, and fluid and electrolyte imbalance, referred to as "fistula triad", significantly increase the risk of mortality and significantly reduce the rate of spontaneous fistula closure.[2] Patients with ECF are at high risk of malnutrition due to decreased food intake, ineffective nutritional therapy resulting from a large number of nutrients that come out along with enteric secretions, and changed metabolism caused by the underlying disease.[5,6]

Optimal ECF management involves a multidisciplinary team, consisting of surgery, nutrition, nursing, and pharmacy departments. Institutions with sufficient experience and appropriate ECF treatment can reduce the mortality rate by up to 50%.[1] In terms of prognosis, it is found that patients experiencing no malnutrition are 15 times greater to have spontaneous closure of fistulas.[7,8] As cited from Davis KG et al, the rate of fistula closure is also twice lower in patients who do not receive nutritional interventions than in those who receive nutritional interventions.[4] Thus, it is crucial to comprehend a step-by-step approach of nutrition management in order to reduce the rates of both morbidity and mortality in ECF cases.

Step-by-Step approach in ECF nutrition management

In ECF nutrition management, fluid resuscitation, electrolyte imbalance correction, and sepsis control have to be conducted before nutrition is given to ECF patients.[1] However, it is important that a nutrition plan has previously been well prepared for them. In this regard, nutrition management typically includes assessing patients' nutritional status, selecting the nutrition routes, determining macronutrients, micronutrients, and specific nutrients, providing pharmacotherapy, and carrying out monitoring and evaluation. These proposed steps are presented in **Figure 1**.

1. Assessing patients's nutritional status

Malnutrition screening has to be done at the beginning of the diagnosis. If malnutrition is not detected during the initial diagnosis, periodic screening then becomes necessary. To date, no malnutrition screening methods are validated explicitly for use under ECF conditions.[11] Some of the validated screening tools that can be used easily are Nutritional Risk Screening (NRS) 2002, Malnutrition Universal Screening Tool (MUST), and Subjective Global Assessment (SGA).[16]

Patients with ECF often experience malnutrition caused by the underlying disease, decreased food intake, increased protein requirements associated with systemic inflammation, and increased nutrient loss associated with the amount of fistula output. Nutritional status functions principally as a predictor of spontaneous fistula closure. According to de Aguilar-Nascimento, et al., patients with no malnutrition are 15 times greater to have spontaneous closure of fistulas (OR = 15.4 [95% CI = 1.1-215.5]; p = 0.04).[8]

Despite being frequently measured before and during nutritional therapy of ECF patients, serum protein levels do not function as a marker for sensitive nutritional status. Decreased concentrations of serum plasma albumin, transferrin, retinol-binding proteins, and prealbumin are likely a consequence of systemic inflammation associated with ECF.[11] Besides, albumin levels can be found to be extremely high in ECF patients due to decreased plasma volume, especially in high-output fistulas.[17] Prealbumin, also known as transthyretin, is an acute negative visceral protein and reactant that is normally influenced by the same factors affecting albumin levels. Nonetheless, it is more recommended than albumin due to having a relatively short half-life of 2 days. Subsequently, prealbumin concentrations can become a predictor of recent food intake.[18] This means that serum protein concentrations obtained before and during nutritional therapy can not be used as a marker of the nutritional status, but as an indicator of the prognosis.[11]

2. Stabilizing patients through rehabilitation phase

As regards with rehabilitation phase, oral nutrition is normally stopped (nil per os, NPO), and nutrition is given through total parenteral nutrition (TPN). TPN should be given within a short duration to reduce the risk of complications, especially if given through a central route with a target nutritional requirement of 30-40 ml/kg of fluid, 30-40 kcal/kg of calories, and 1.5-2 g/kg of protein. The strict control of blood glucose levels is needed to avoid the occurrence of hyperglycemia. The ratio of carbohydrates, fats, and proteins in TPN can be modified according to patients' medical histories.[3] When hemodynamics are stable, it is advisable to immediately provide enteral nutrition (EN) to prevent villous atrophy, which is also termed as "gut feeding". Clear liquid diets can be given as an option during gut feeding, with components that provide energy, electrolytes, and no concentrated or carbonated sweeteners and leave minimal residues in the gastrointestinal tract. Examples of clear liquid diets include broth, coffee, tea, sugar-free gelatine, or drinks with alternative sugars.[9]

3. *Determining patients' nutrition requirements*

Nutrition routes

Nutritional routes should be selected based on various considerations, including the location of fistulas, the length of the healthy intestine for nutrient absorption, the signs of distal obstruction, and the amount of fistula output. An in-depth assessment of fistula characteristics (e.g., anatomical position and length) is required. In ECF cases without distal obstruction, patients with low output (<500 mL/day) can tolerate an oral diet. If oral food intake is associated with a significant increase in ECF output or is not tolerated by patients for other reasons, EN can be tried and tolerated when enteral access can be obtained. Relative contraindications to EN include insufficient intestinal length (75cm), intestinal discontinuity, intolerance of symptoms to enteral nutrition, increased fistula output leading to electrolyte disturbances at the beginning of enteral nutrition, and inability to maintain food access.[6]

Patients' EN tolerance and ability to achieve the target intake must be evaluated on a daily basis. If nutritional goals cannot be achieved only with EN, combined nutrition therapy of EN and PN can be initiated. High-calorie supplementary drinks can also be an alternative to meeting patients' calorie requirements.[1] Besides having advantages in terms of lower cost and reduced risk of infection, administration of at least 20% of nutrients through enteral nutrition can help maintain intestinal flora, reduce bacterial translocation, and maintain mucosal integrity and immune function.[10]

ECF patients with high output (>500 mL/day), experiencing intestinal obstruction, ECF drainage that significantly worsens wound conditions and skincare or interferes with the ability to maintain fluid and electrolyte balance when EN is used, require parenteral nutrition (PN) to meet nutritional needs to support spontaneous or surgical ECF closure.[11] Some contraindications to PN administration are impaired liver function, difficulty in vascular access, or infection in the vicinity of the vascular access location. In general, PN is required in most high-output ECF patients, although it is only in the early phase, and it has been used to reduce ECF output secretion by 30% to 50% and contribute to ECF closure.[12] The flow path of selecting nutritional pathways for ECF patients is provided in **Figure 2**.

An oral route can be chosen for ECF patients with high output, with the following modifications: i) limiting low sodium fluid intake to 500mL/day, ii) providing patients with high sodium oral solution (90-120 mmol/L sodium level), iii) giving nutrition in forms of solid food and fluid in a small amount, and iv) providing combined administration of proton pump inhibitors, antimotility drugs, and octreotide.[13] Home Parenteral Nutrition (HPN) is recommended when patients are medically stable and fistula output can be managed. The example can be taken from patients awaiting surgeries.[11]

Fistuloclysis is defined as "a technique using fistulas as the main enteral pathway for access and entry of food ingredients, formulas, or gastrointestinal secretions". Fistulas are a low-cost method compared to the use of standard polymer nutrients instead of PN, but are rarely performed because of technical, anesthetic, and patient comfort issues. Fistuloclysis technique requires the presence of experienced medical personnel for the installation in order for the food hose to remain stable, unleaked, and unattracted by peristalsis. Leakage of fistuloclysis will cause skin corrosion, thus allowing for infection. Fistuloclysis can stimulate fistula epithelialization, so it can reduce the possibility of spontaneous closure of fistulas.[12] Therefore, fistuloclysis is only recommended in fistulas which are predicted not to close spontaneously. In the administration of initial fistuloclysis, it is recommended to use a polymer formula, which can be converted into an oligomeric diet if intolerance occurs.[11]

The volume of ECF output also needs to be taken into consideration. Generally, fistuloclysis can be used an option in ECF cases when the location is proximal to ensure that nutrition can still be absorbed sufficiently or when TPN administration is not applicable or contraindicated. As stated by Coetzee et al.14, re-administration of chyme through fistuloclysis does not cause side effects and can be considered to increase enteral feeding tolerance and maintain fluid and electrolyte homeostasis. Although fistuloclysis is normally carried out in low-output ECF, Niu et al. 15 stated that in high-output ECF cases (in 1500-2000 mL/day), nutritional administration through fistuloclysis can be conducted by percutaneous enterostomy over a long period of time and can provide good clinical outcome.

Energy requirements

Energy requirements should be assessed for patients with ECF. In this regard, the most accurate method for calculating energy requirements is by using indirect calorimetry. If indirect calorimetry is not applicable, the Harris-Benedict equation can be used to calculate nutrient requirements. ECF patients typically have catabolic and hyper-metabolic conditions. Basal energy requirements can be estimated using the Harris-Benedict equation with a modification of 1 to 2.5 times from basal energy requirements of healthy adults, depending on the amount of output.[1] According to the ESPEN recommendation, the guidelines outlined in the Rules of Thumb can also be applied to ECF patients who have complications of intestinal failure, i.e., energy requirements of 25-35 kcal/kg/day, depending on patients' clinical conditions.[19]

In obese patients with ECF, nutrition can be given to critical patients according to the guidelines set by ASPEN and Society of Critical Care Medicine (SCCM). For instance, requirements vary from 11 to 14 kcal/kg of body weight per day if BMI is in the range of 30-50kg/ m2; and requirements range from 22 to 25 kcal/kg of body weight per day if BMI is more than 50kg/m^2.[20]

Macronutrient needs

In patients with ECF, the amount of protein loss through enteric secretion can reach 75 grams a day.[1] The provision of protein in ECF patients is based on the amount of output produced by enteric secretion. However, it can be given 1.5-2.0 g/kg/day in general. In patients with entero-atmospheric fistulas and high-output ECF, protein administration can stand at 2.5 g/kg/day.[11] In obese patients with ECF, protein administration of 2g/kg of body weight per day is recommended for patients with BMI at a range of 30-40kg/m^2; and protein administration of 2.5 g/kg of body weight per day for those with BMI of >40 kg/m^2.[20] To date, there are no specific recommendations regarding carbohydrate and fat requirements for ECF patients.

Micronutrient needs

Vitamins and minerals are wasted because of either enteric fluid secreted by ECF patients or impaired absorption associated with gastrointestinal dysfunction. As a result, deficiencies for these types of micronutrients can be predicted by examining the anatomical digestive dysfunction that occurs in patients. Fistulas that take place in the proximal jejunum, for example, are likely to make them suffer from deficiencies of fat-soluble vitamins and water-soluble vitamins. However, if fistulas are situated in the ileum, particularly before 50-60 cm of terminal ileum, they will have deficiencies of vitamin B12 and fat-soluble vitamins. In this case, vitamin B12 needs to be injected. Besides, patients will get exposed to suffering from zinc and vitamin C deficiencies. With high-output ECF, patients will also be prone to have magnesium deficiency. Consequently, administration of intravenous magnesium sulfate or oral magnesium chloride can be given to increase enteral absorption.[2] In relation to this, it is suggested to administer twice the standard requirements for vitamins and minerals and five to ten times the standard requirements for zinc and vitamin C, especially for high-output fistulas.[1]

Specific nutrients

As regards with specific nutrients, there is no certain advice on the use of immunonutrient formulas due to inadequate evidence. However, oral glutamine supplementation has been used to reduce the rate of mortality and increase the closure of fistulas. Glutamine, apart from being the main nutrient of intestinal cells, plays an important role in the immune system by increasing secretory IgA production in the intestinal mucosa.[11] As said by de Aguilar-Nascimento, et al.[8], fistula resolution is 13 times greater in patients receiving oral glutamine of 0.3 g/kg/day in addition to PN (OR = 13.2 (95% CI = 1,1-160.5); p=0.04). Nevertheless, glutamine metabolism will not be optimal in individuals with kidney, liver, or sepsis failure, since they have a higher risk of toxicity.[11] According to a study by Martinez et al.[21], enteral administration of 4.5 g of arginine and 10 g of glutamine in a preoperative ECF patient for seven days can reduce the recurrence risk and the inflammatory cytokines for one week postoperatively. Other immunonutrient supplements such as arginine, omega-3 fatty acids, and nucleotides have yet to be proven in ECF cases.[16] Omega-3 is regularly indicated in critically ill patients, yet the current evidence gives rise to controversy.[22–24]

4. Providing patients with pharmacotherapy

In adult patients with high-output ECF, administration of somatostatin and somatostatin analogs is recommended as a method to reduce effluent drainage and increase spontaneous closure. In relation to somatostatin, it has a very short half-life of 1-2 minutes and is naturally produced in the pancreas of the digestive tract. Besides, octreotide is an example of somatostatin analogs and has a much longer half-life of 113 minutes. Somatostatin and somatostatin analogs can inhibit the release and secretion effects of varying gastrointestinal hormones and increase the absorption of water and electrolytes, thus extending the intestinal transit time and, eventually, reducing the volume of gastrointestinal secretions.[11]

Despite the support of varied meta-analyses[25–27] to the effectiveness of using somatostatin and somatostatin analogs in increasing the likelihood of spontaneous closure, de Vries, et al.[28] mentioned that somatostatin and its analogs are not conclusive in their benefits for reducing fistula output. In the study, three classes of drugs, namely proton pump inhibitors, antimotility agents (loperamide), and histamine receptor antagonists, can reduce fistula output effectively with a confidence level of 2b.

5. Carrying out monitoring and evaluation

Some of the benchmarks for successful nutritional management in ECF cases include achieving an anabolic state, which is regularly signaled by weight gain and increased levels of albumin, prealbumin, and transferrin, and meeting the needs of micronutrients for optimal healing.[1] Albumin, prealbumin, and transferrin themselves are acute-phase proteins whose levels are not accurate under conditions of acute stress and sepsis. Serum albumin is the most common plasma protein, representing about 50% of the total protein content (3.5-5 g/L). Albumin production in the liver is regulated by osmolarity and oncotic pressures. It is stimulated by hormonal factors (insulin, cortisol, and growth hormone) and is inhibited by acute-phase cytokines, such as interleukin (IL) -6 and tumor necrosis factor (TNF)-α. Futhermore, prealbumin and albumin levels provide an indirect assessment of visceral protein storage, while transferrin is the main iron transport protein in plasma. Albumin and transferrin levels have been used to predict the rates of spontaneous closure and mortality.[1] Spontaneous fistula closure is 18.1-fold greater in ECF cases with improvement in serum albumin compared to those without repair.[8] Prealbumin levels can function as an indicator of nutrition, followng that they can describe the adequacy of protein due to a very short half-life.[18,2] The use of the c-reactive protein (CRP) test is not specific in ECF cases, but can be used in conjunction with prealbumin. The ratio of CRP to prealbumin has been validated to be prognostic to spontaneous closure of fistulas. For patients with a ratio of less than or equal to 0.2, fistula closure occurs in 87.0% (95% CI, 74.0-94.3), whereas for patients with a ratio of greater than 1.0, no fistulas are closed.[17]

Anthropometry evaluation in ECF cases is given to body weight, body mass index (BMI), mid-upper arm circumference (MUAC), and thick skin folds. The measurement of MUAC can provide a more accurate estimate in patients with edema. For patients with unstable fistula output, there is a high risk of dehydration, causing the results of weight measurements to become biased. The same condition arises for bioelectrical impedance analysis (BIA). This examination will only be accurate in individuals with stable fluid balance because it is influenced by body cell mass, integrity, and function of cell membranes.[11] Nonetheless, anthropometric and biochemical tests (electrolytes, hemoglobin, CRP, IL-6, albumin) are still recommended to monitor the risk of dehydration and malnutrition.

Intake tolerance needs to be evaluated to assess the provided nutritional therapy and supplemental nutrition. The clinical symptoms of refeeding syndrome also have to be evaluated in patients, especially those with malnutrition. In this regard, malnutrition screening needs to be done regularly to identify the presence of malnutrition as early as possible, as given in Chapter 2.2.[11] Patients receiving enteral nutrition through either duodenum or jejunum are at risk for developing dumping syndrome's symptoms.

When patients receive EN, their tolerance to EN and ability to achieve the target intake must be assessed daily.[11] The lipid profile can be examined from ECF patients, especially those receiving PN. Increased triglyceride levels are frequently found in ECF cases, which can lead to dysregulated immune system, heart and lung functions, and increased liver steatosis. As stated by Visschers et al.[29], sepsis, PN, high-output small intestinal fistula, and inflammatory bowel disease are independent risk factors for hypertriglyceridemia. In clinical practices, triacylglycerol containing long-chain fatty acids (LCFA) is a major component of PN in PN lipids. The transport of LCFA depends on the carrier protein in the cell membrane, which is responsible for transporting fatty acids into cells and mitochondria to undergo oxidation. Increased levels of LCFA that are beyond the amount of carrier protein will result in accumulation, manifested by liver steatosis.

Nitrogen balance has a clinical significance, which indicates patients' anabolic status.[1] It can be calculated by assessing the amount of nitrogen intake and nitrogen output. To do this, urine needs to be stored for 24 hours to calculate the urine urea nitrogen level. Nitrogen balance will be meaningful only if patients experience sepsis resolution. If the value is negative, this indicates that the nutritional therapy given needs to be evaluated and modified. In ECF cases, a correction factor in the calculation of nitrogen balance due to protein loss through fistula output must be considered with additional 1g of nitrogen output for every 500 ml of fistula output.[30] The modified nitrogen balance equation in ECF patients applies as follows: Nitrogen balance = [Protein intake (g) ÷ 6,25] - urine urea nitrogen (NUU) + 4 g + (2 g × amount of enteric fluid loss in liters)].[12]

Citrulline, a non-essential amino acid produced by enterocyte cells, has high sensitivity and specificity to predict permanent bowel failure when the serum level is below 20 mol/L. Citrulline is also an alternative biomarker to assess the intestinal length that is functional for absorption.[18]

If fistulas do not close spontaneously within 30 to 40 days or they cannot close due to various comorbidities, surgery should be considered immediately by maintaining the nutritional support. Aside from this, an acronym is commonly used to remember the factors that complicate spontaneous closure, namely "FRIEND". This acronym stands for F - Foreign body; R - Radiation; I - Inflammation or infection; E - Epithelialization of the fistula tract, N - Neoplasm; and D - Distal obstruction.[31]

Based on the location, spontaneous closure is more likely to occur in upper gastrointestinal fistulas (proximal to the duodenojejunal flexure). Fistulas located in the upper gastrointestinal tract are generally side fistulas without any residual disease of the gastrointestinal tract. These fistulas differ from lower gastrointestinal fistulas that are commonly associated with Crohn's disease, radiation enteritis, or ischemia. Although the rates of spontaneous closure vary considerably between upper and lower gastrointestinal fistulas, their rates of mortality are quite similar.[32]

Conclusion

Enterocutaneous fistula (ECF) management requires a multidisciplinary team as an approach to achieve an optimal clinical output. The purpose of nutritional medical therapy in ECF cases is to adequately estimate nutritional needs, maintain fluid and electrolyte balance, and stimulate spontaneous ECF closure whenever possible. To achieve an optimal outcome, an analysis of nutrition needs has to be conducted individually by considering the etiology, the anatomical fistula location, and the amount of output. This appears to be so important that the selection of nutritional pathways, the regulation of macronutrient and micronutrient requirements, the use of specific nutrients, and the provision of pharmacotherapy can be made with the right indications.

It is preferred that EN therapy is provided in ECF cases with low output, proximal location, and no distal obstruction. However, combined nutrition therapy of EN and PN can be initiated if the intake cannot be toleranced. Energy requirements should be measured by using indirect calorimetry. If indirect calorimetry is not applicable, it can be altered to other standard equations such as the

Harris-Benedict or the Rules of Thumb. As regards with the provision of protein, it is given 1.5-2 g/kg/day based on patients' clinical considerations. Micronutrient supplementation may be needed in cases of high-output fistulas. Glutamine and specific nutrients can increase the likelihood of spontaneous closure of fistulas and are associated with a better postoperative output. For instance, pharmacotherapy, somatostatin, and its analogs are recommended in high-output ECF cases.

In addition, evaluation and monitoring have to be carried out regularly in order to identify complications, particularly for sepsis, dehydration, and malnutrition. Anthropometric assessments to daily body weight, fluid balance, nitrogen balance, vital signs, and biochemistry (prealbumin, CRP, lactate, lipid profile, organ function, and electrolytes), also function as essential indicators to determine the success of nutrition therapy.

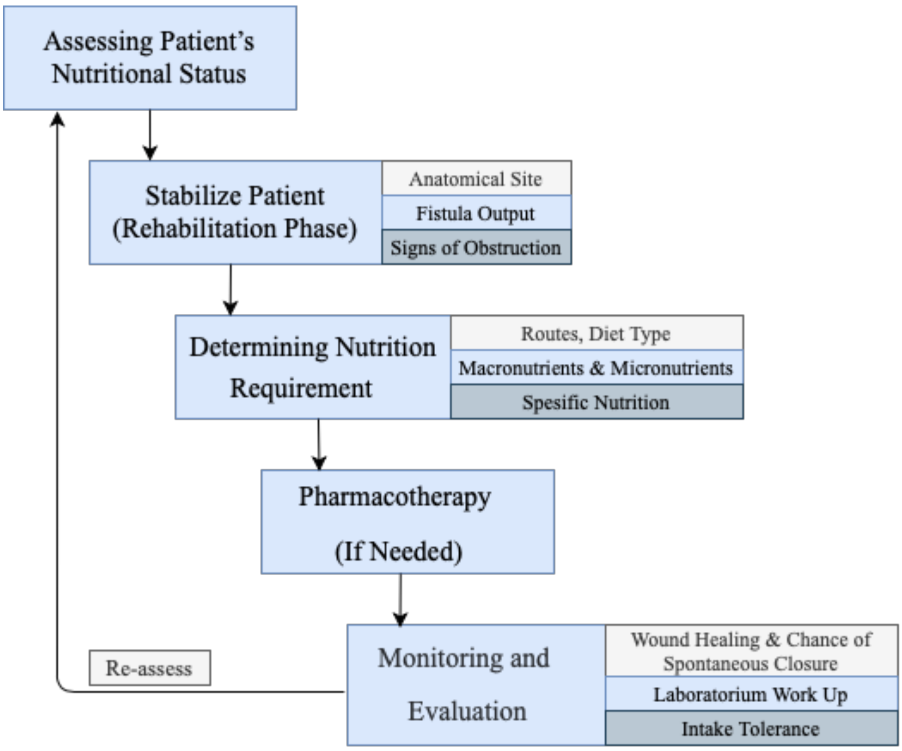

Figure 1. Proposed algorithm of nutrition management in enterocutaneous fistula.

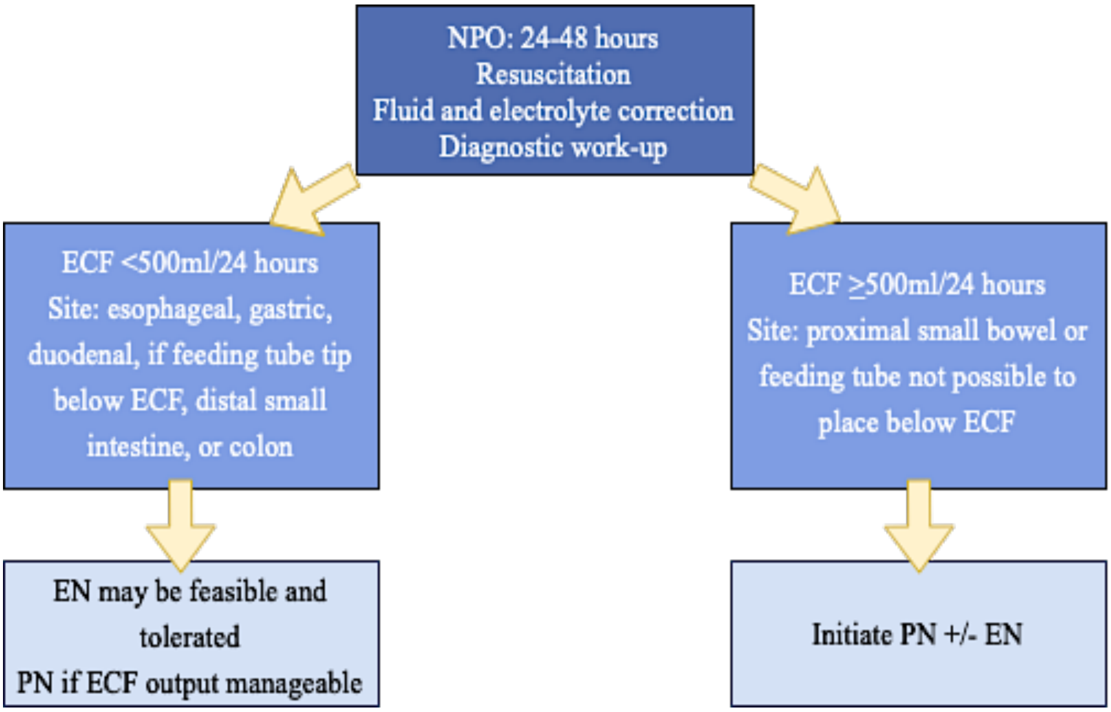

Figure 2. Routes of Nutrition Support Consideration. ECF: enterocutaneous fistula; EN: enteral nutrition; PN: parenteral nutrition. (Adapted from Kumpf VJ, de Aguilar-Nascimento JE, Diaz-Pizarro Graf JI, Hall AM, McKeever L, Steiger E, et al. ASPEN-FELANPE Clinical Guidelines: Nutrition Support of Adult Patients With Enterocutaneous Fistula. J Parenter Enter Nutr. 2017;41:104–12)

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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